

WHAT IS CLAIMED IS:

1 1. A method of measuring a response to a stimulus of a plurality of
2 samples spots of a sample using a measuring system having a measurement range to generate
3 an image of the sample in digital space, the method comprising:

4 for each sample,
5 while measuring the response, varying the stimulus to include at least
6 one stimulus value where the measured response corresponds to a value in an
7 intermediate portion of the measuring range, and
8 storing a value of the measured response that corresponds to a value in
9 the intermediate portion of the measurement range, and the stimulus value that
10 produced that value of the measured response.

1 2. The method of claim 1, and further comprising dividing each stored
2 value of the measured response by the corresponding stimulus value to provide a
3 normalized-response value.

1 3. The method of claim 2, and further comprising, for each normalized-
2 response value, multiplying each normalized-response value by a highest stimulus value that
3 is stored to generate the image, wherein these normalized-response values that are multiplied
4 by the highest stimulus value that is stored are referred to as the image spots.

1 4. The method of claim 3, wherein the image spots form the image in
2 digital space.

1 5. The method of claim 3, wherein the steps of varying the stimulus and
2 storing the value of the measured response are performed in one scan of the sample.

1 6. The method of claim 5, wherein the scan includes a raster scan of each
2 row of the sample spots.

1 7. The method of claim 3, wherein the image includes a microarray image
2 of a microarray.

1 8. The method of claim 3, wherein the measuring system includes an A/D
2 converter having a particular number of bits that accommodates a particular range of
3 response values.

1 9. The method of claim 8, wherein at least one of the image spots has a
2 number of bits that exceeds the particular number of bits of the A/D converter.

1 10. The method of claim 1, wherein a variation of the measured responses
2 over the plurality of samples exceeds the measurement range.

1 11. The method of claim 1, wherein varying the stimulus includes
2 increasing the stimulus over a range.

1 12. The method of claim 11, wherein increasing the stimulus includes
2 increasing the intensity of laser radiation.

1 13. The method of claim 1, wherein for multiple ones of the plurality of
2 sample spots, the value in the intermediate portion of the measurement range is
3 approximately the same value.

1 14. The method of claim 1 wherein:
2 the samples spots are regions having probes hybridized with targets having
3 fluorescent tags;
4 the stimulus is visible or UV optical radiation; and
5 the response is a level of fluorescent emission.

1 15. The method of claim 14, wherein the stimulus is laser radiation.

1 16. The method of claim 1 wherein:
2 the stimulus is electromagnetic radiation; and
3 the response is a level of reflected radiation or transmitted radiation.

1 17. A method of acquiring image-response values for an extended sample
2 subjected to a stimulus to generate an image in digital space that includes the image-response
3 values, the method comprising:

4 for each of a plurality of spots,
5 subjecting the sample to a plurality of stimulus values in a single scan
6 of the spots,
7 measuring corresponding response values,

8 determining a stimulus value that provides a response value within a
9 desired range, and
10 storing the stimulus value, so determined, and the response value
11 provided by that stimulus value;
12 providing a normalized data set for the plurality of spots where each
13 spot's normalized value represents a ratio of the stored response value and the
14 corresponding stimulus value.

1 18. The method of claim 17, wherein the step of providing the normalized
2 data set for the plurality of spots includes multiplying the normalized values by a highest
3 stored stimulus value, and these values are the image-response values.

1 19. The method of claim 17, wherein the desired range is an intermediate
2 range of an A/D converter having a particular number of bits that accommodates a particular
3 range of response values, and at least one of the image-response values has a number bits that
4 exceeds the particular number of bits of the A/D converter.

1 20. A method for generating a microarray image of a sample that includes
2 a plurality of microarray spots irradiated with laser radiation, such that radiation from each
3 microarray spot is a response to being irradiated, the method comprising:

4 for each microarray spot in a single scan of the microarray:
5 varying an intensity value of the laser radiation within a range of
6 values,
7 storing a radiation value for the radiation, and a corresponding
8 intensity value for that radiation value, wherein the radiation value is below a
9 saturation level of a detector, and
10 dividing the stored radiation value by the stored intensity value to
11 generate a normalized-radiation value; and
12 multiplying the normalized-radiation values by a highest radiation value that is
13 stored.

1 21. The method of claim 20, wherein the detector includes an A/D
2 converter configured to generate the radiation values, and the saturation level is a saturation
3 level of the A/D converter.

1 22. The method of claim 21, wherein the normalized-radiation values
2 multiplied by the highest radiation value this is stored are independent of a measurement
3 range of the A/D converter.

1 23. The method of claim 20, wherein the stored radiation values are in a
2 central portion of a measurement range of the detector.

1 24. The method of claim 20, wherein the stored radiation values vary by
2 about +/- 20%.

1 25. The method of claim 20, wherein the detector includes a radiation-
2 detection that is at least one of a photomultiplier tube, an avalanche photodiode, a CCD
3 (charge coupled device) array, a CMOS (complementary metal oxide) array.

1 26. The method of claim 20, wherein the stored radiation values are
2 approximately the same.

1 27. The method of claim 20, wherein the laser radiation is excitation-laser
2 radiation, and the radiation is fluorescent radiation.

1 28. The method of claim 27, wherein the excitation-laser radiation has a
2 first wavelength and a second wavelength.

1 29. The method of claim 28, wherein the first wavelength is a red
2 wavelength and the second wavelength is a green wavelength.

1 30. The method of claim 28, wherein:
2 the microarray image includes a first microarray image and a sub-microarray
3 image,
4 the first microarray image is associated with the first wavelength, and
5 the sub-microarray image is associated with the second wavelength.

1 31. The method of claim 20, wherein the radiation is backscattered
2 radiation.

1 32. The method of claim 20, wherein the step of storing the radiation value
2 includes storing the radiation values and the intensity values in a memory at memory
3 addresses that correspond to coordinate positions of the microarray spots on the sample.

1 33. The method of claim 20, further comprising digitally operating on the
2 normalized-radiation values with a mathematical function.

1 34. An image generator for generating a digital-space image of a sample
2 comprises:

3 a radiation source configured to generate radiation and irradiate sample spots
4 of the sample, wherein the sample spots radiate in response to being irradiated;

5 a modulator configured to modulate an intensity of the radiation;

6 a detector having a measurement range and configured to generate radiation
7 values from the radiation from the sample spots;

8 a memory configured to store a radiation value that corresponds to an
9 intermediate portion of the measurement range, and a radiation value for the generated
10 radiation that corresponds to that radiation value; and

11 a processor configured generate image spots of the digital-space image by
12 normalizing the stored radiation values by their associated radiation values of the generated
13 radiation and multiplying these values by a highest radiation value of the generated radiation
14 this is stored the digital-space image.

1 35. The generator of claim 34, wherein the detector includes an analog-to-
2 digital (A/D) converter configured to generate the radiation values, and the intermediate
3 portion of the measurement range is an intermediate portion of the measurement range of the
4 A/D converter.

1 36. The generator of claim 35, wherein the A/D converter has a particular
2 number of bits that accommodates a particular range of radiation values.

1 37. The generator of claim 36, wherein at least one of the image spots has
2 a number bits that exceeds the particular number of bits of the A/D converter.

1 38. The method of claim 35, wherein the image spots are independent of a
2 measurement range of the A/D converter.

1 39. The generator of claim 35, wherein the detector includes a radiation-
2 detection configured to detect the radiation, and the radiation detector includes at least one of
3 a photomultiplier tube, an avalanche photodiode, a CCD (charge coupled device) array, and a
4 CMOS (complementary metal oxide) array.

1 40. The generator of claim 39, and further comprising an amplifier-filter
2 module configured to amplify and filter output of the radiation detector and provide amplified
3 and filtered output to the A/D converter.

1 41. The generator of claim 34, wherein the processor is configured to
2 multiply the normalized-radiation values by a highest laser-radiation value to generate the
3 microarray image.

1 42. The generator of claim 34, wherein the processor is a RISK (reduced
2 instruction set) microprocessor.

1 43. The generator of claim 34, wherein the intensity modulator includes at
2 least one of an electrooptic modulator disposed between a pair of crossed polarizers, an
3 acoustooptic modulator, and a controllable variable-neutral-density filter.

1 44. The generator of claim 34, and further comprising a lens system
2 configured to focus the laser radiation on the sample spots and collect the radiation from the
3 sample spots for collection by the detector.

1 45. The generator of claim 34, and further comprising a second laser
2 configured to irradiate the sample spots with laser radiation having a wavelength different
3 from the laser radiation of the first mentioned laser to generate a second microarray image.

1 46. A method for generating an image of a sample that includes a plurality
2 of spots irradiated with stimulus radiation, such that response radiation from each spot is a
3 response to the stimulus radiation, the method comprising:

4 for each spot, in a single scan of the sample:
5 varying an intensity value of the stimulus radiation within a discrete
6 range of values,

7 storing a radiation value for the response radiation and an attenuation
8 state for that radiation value, wherein the radiation value is within a measurement
9 range of a detector, and each attenuation state is associated an attenuation value, and
10 normalizing the radiation values based on the attenuation values to
11 form the image in digital space.

1 47. The method of claim 46, wherein the detector includes an A/D
2 converter configured to generate the radiation values, and the measurement range is above a
3 measurement level.

1 48. The method of claim 47, wherein the measurement level is at least ten
2 percent above a threshold level of the A/D converter.

1 49. The method of claim 46, wherein the stimulus radiation is laser
2 radiation, and the response radiation is fluorescent radiation.

1 50. The method of claim 46, wherein the response radiation is
2 backscattered radiation.

1 51. The method of claim 46, wherein the step of storing the radiation value
2 includes storing the radiation values in a memory at memory addresses that correspond to
3 coordinate positions of the spots on the sample.

1 52. The method of claim 46, further comprising digitally operating on the
2 image with a mathematical function.